AQUEOUS COMPOSITIONS CONTAINING CORTICOSTEROIDS FOR NASAL AND PULMONARY DELIVERY

FIELD OF THE INVENTION

The present invention relates to pulmonary drug delivery compositions useful for the inhaled administration of corticosteroid compounds and the method of their administration. The delivery compositions are useful for the treatment of ailments and diseases of the lungs. Similar corticosteroid compositions may be used for nasal delivery.

BACKGROUND OF THE INVENTION

Delivery of therapeutic compounds directly to affected lung tissues has several advantages. The drug reaches the target tissue without first entering the systemic circulation and being subjected to dilution by the blood, binding to blood components, or metabolism by the liver and excretion by the kidneys. A high local concentration of drug can be achieved in the lungs while the systemic concentration is kept below that likely to cause adverse side effects. In addition, the apical side of the lung tissue – the side exposed directly to inspired air – can be treated with compounds that might not readily cross the endothelium or epithelium, which form barriers between the apical surface and the blood plasma. Similar considerations apply to the tissues lining the nasal passages and sinus cavities.

Several means have been developed to deliver compounds directly to the passages of the lung or nose. The most common form, especially for water-insoluble

formulation is typically nebulized. Considerations of particle size mentioned above also apply to the droplet size of the mists. However, it is possible to rebreathe a portion of the mist during several minutes of treatment and increase the capture of the fine droplet fraction that can penetrate the lung most deeply. In addition, there is no need for coordination between hand action and breathing, making the nebulizer easier to use for patients. It may be possible, in some cases, to administer drugs not soluble in aqueous solution by nebulizing them in suspension. However, the droplet size of nebulized drug-containing suspensions cannot be smaller than that of the suspended particles. Therefore, the finer droplets produced from these systems would not contain any drug.

Thus, one limitation of nebulized formulations is that they are most suitable for those drug compounds that are sufficiently water soluble such that a therapeutic dose of the drug can be dissolved in from 1 to about 3 mL of aqueous solution. One way around this limitation is to formulate with polar organic solvents or aqueous solutions thereof. However, few organic solvents can be safely inhaled for prolonged periods. Most organic solvents that are currently approved for use in inhalation devices are propellants, such as chlorofluorocarbons (CFCs), which will soon be eliminated from manufacturing for environmental reasons, or the newer hydrofluorocarbons and low boiling hydrocarbons, all of which are expected to evaporate prior to penetrating the lungs. Such solvents can evaporate rapidly during nebulization and leave the drug behind in the device or in large particles that would be likely to be deposited in the mouth or throat rather than be carried to the lungs. Indeed, MDIs were developed to circumvent such problems.

Another way to overcome the solubility problem of the drug is to blend cosolvents such as ethanol, propylene glycol, or polyethylene glycol with water. However, there are limits to acceptable levels of these cosolvents in inhaled products. Typically, the cosolvents make up less than about 35% by weight of the nebulized composition, although it is the total dose of cosolvent as well as its concentration that determines these limits. The limits are set by the propensity of these solvents either to cause local irritation of lung tissue, to form hyperosmotic solutions which would draw fluid into the lungs, and/or to intoxicate the patient. In addition, most potential hydrophobic therapeutic agents are not sufficiently soluble in these cosolvent mixtures.

Thus, there is a need to develop improved systems that can solubilize water-

immunosuppression and imbalances in mineral metabolism. The corticosteroids commonly used in asthma treatment have a high ratio of topical to systemic potency. That is, these corticosteroids are highly active when delivered directly to the site of inflammation but relatively inactive when passed through the systemic circulation. The portion of an inhaled dose which is swallowed and absorbed through the intestine or absorbed through the lung tissue into the circulation is subjected to metabolism by the liver and converted to less active compounds with short half-lives. These metabolites are quickly eliminated from the blood, reducing the incidence of systemic side effects.

Among the most commonly used steroids are aldosterone, beclomethasone, betamethasone, budesonide, cloprednol, cortisone, cortivazol, deoxycortone, desonide, desoximetasone, dexamethasone, difluorocortolone, fluclorolone, flumethasone, flunisolide, fluocinolone, fluocinonide, fluocortin butyl, fluorocortisone, fluorocortolone, fluorometholone, flurandrenolone, fluticasone, halcinonide, hydrocortisone, icomethasone, meprednisone, methylprednisolone, mometasone, paramethasone, prednisolone, prednisone, tixocortol, triamcinolone, and others, and their respective pharmaceutically acceptable derivatives, such as beclomethasone diproprionate, dexamethasone 21-isonicotinate, fluticasone propionate, icomethasone enbutate, tixocortol 21-pivalate, triamcinolone acetonide, and others. Fortunately, some of these synthetic steroids have low potentials for systemic absorption because of their unique structures and metabolism.

Corticosteroids have usually been formulated as suspensions of micronized drug powder in chlorofluorocarbon vehicles or with chlorofluorocarbon-free propellants and delivered by metered dose inhaler. The choice of this type of carrier and apparatus was dictated by the fact that corticosteroids are very difficult to stabilize in aqueous media and frequently produce systems that exhibit crystal growth, precipitation, and/or aggregation of suspended or solubilized drug.

Corticosteroids have been formulated in different drug delivery systems for administration to the respiratory tract. U.S. Patent 5,292,499 relates to reverse micelle colloidal dispersions of hydrophilic pharmaceutically active compounds prepared with aerosol CFC propellant formulations useful for topical, endopulmonary, nasal, or inhalation administration.

U.S. Patent 5,208,226 describes the concept of using a novel combination

SUMMARY OF THE INVENTION

The present invention provides compositions suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract and methods for the administration of said compositions.

In one embodiment, the corticosteroid composition contains from about 0.1 to about 20 percent by weight of a high-HLB surfactant component (HLB greater than about 10), for example, ethoxylated derivatives of Vitamin E such as tocopheryl polyethylene glycol 1000 succinate ("TPGS"). The HLB, or hydrophilic-lipophilic balance, is a measure on an arbitrary scale of the polarity of a surfactant or mixture of surfactants. For example, TPGS has an HLB between about 15 and 19. Generally, the corticosteroid composition contains the corticosteroid in an amount from about 5 μg/ml to about 1 mg/ml. The composition is aqueous-based, containing at least about 70 weight percent of an aqueous phase that can include buffering, tonicity, taste-masking, and preservation additives.

The corticosteroid composition can also contain one or more pharmaceutically acceptable cosolvents to aid in the processing of the composition and to increase the solubility of the corticosteroid. Such cosolvents include mono- and polyvalent alcohols, such as propylene glycol, ethanol, and polyethylene glycol. Optionally, the corticosteroid compositions also can contain such components as low-HLB surfactants (HLB below about 8) and/or oils. Low-HLB surfactants include phospholipids, medium-chain mono- and diglycerides, and mixtures thereof. Useful pharmaceutically acceptable oils include triglycerides and propylene glycol diesters of medium-chain fatty acids.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compositions containing corticosteroid compounds as active agents for the treatment of ailments and diseases of the respiratory tract, particularly the lungs, by way of nasal and pulmonary administration. The compositions can be formulated such that they contain the corticosteroid active agent(s) in a dissolved state. The formulations can be stored either in a concentrated form to be diluted at the time of use or a ready-for-use, diluted state. The present invention also sets forth methods for using the compositions for nasal or inhaled delivery.

desoximetasone, dexamethasone, difluorocortolone, fluclorolone, flumethasone, flunisolide, fluocinolone, fluocinonide, fluocortin butyl, fluorocortisone, fluorocortolone, fluorometholone, flurandrenolone, fluticasone, halcinonide, hydrocortisone, icomethasone, meprednisone, methylprednisolone, paramethasone, prednisolone, prednisone, tixocortol, triamcinolone, and their respective pharmaceutically acceptable derivatives, such as beclomethasone diproprionate, dexamethasone 21-isonicotinate, fluticasone propionate, icomethasone enbutate, tixocortol 21-pivalate, and triamcinolone acetonide. Particularly preferred are compounds such as beclomethasone diproprionate, budesonide, flunisolide, fluticasone propionate, mometasone and triamcinolone acetonide.

The corticosteroid compound is present in the final, diluted corticosteroid composition designed for inhalation in an amount from about 5 μg/ml to about 5 mg/ml, preferably from about 10 μg/ml to about 1 mg/ml, and more preferably from about 20 μg/ml to about 500 μg/ml. For example, the preferred drug concentration is between about 20 and 100 μg/ml for beclomethasone dipropionate, between about 30 and 150 μg/ml for triamcinolone acetonide, and between about 50 and 200 μg/ml for budesonide, depending on the volume to be administered. By following the preferred methods of the present invention, relatively high solubilities of the corticosteroid can be achieved in an aqueous-based composition. The solubility of the corticosteroid can be greater than about 50, preferably greater than about 75, and more preferably greater than about 100, in some cases greater than about 150 or about 200, μg/ml.

Similarly, the corticosteroid compound is present in the final, diluted corticosteroid composition designed for nasal administration in an amount from about 50 μg/ml to about 10 mg/ml, preferably from about 100 μg/ml to about 2 mg/ml, and more preferably from about 300 μg/ml to about 1 mg/ml. For example, the preferred drug concentration is between about 200 and 900 μg/ml for beclomethasone dipropionate, between about 250 μg/ml and 1 mg/ml for triamcinolone acetonide, and between about 400 μg/ml and 1.6 mg/ml for budesonide, depending on the volume to be administered.

The corticosteroid composition can also contain various excipients that improve the storage stability of the composition, but which do not significantly affect the overall efficacy of the composition in its freshly prepared state. Such excipients include buffers, osmotic (tonicity-adjusting) agents, low toxicity antifoaming agents, and

phase is preferably water containing the additives necessary to adjust the pH and tonicity, and preservatives if the formulation is intended for multiple use. It is preferred that the aqueous phase be heated prior to the addition of the molten corticosteroid concentrate to aid in dispersion. Generally, the aqueous phase should be heated to about 55-85°C, more preferably from about 60-70°C.

It is preferred that the diluted corticosteroid composition be formulated by first dissolving the drug in the molten TPGS and then dispersing this concentrate in the aqueous phase. If the drug is added to a prediluted mixture of TPGS and aqueous phase, it may not be possible to achieve the final desired concentration of the drug in a dissolved state. To ensure that the drug is solubilized and stable in the diluted composition, it is preferred that the level of the drug in the concentrated composition be from about 1 to about 30 mg/ml, preferably from about 2 to about 20 mg/ml, and more preferably from about 2 to about 10 mg/ml prior to dilution. The level of water in the concentrated corticosteroid composition should be below 5% by weight, preferably below 2% by weight, and more preferably below 1% by weight, and in general, it is advantageous not to add any water to the concentrated corticosteroid composition.

The aqueous phase, which is composed of water and optionally buffering, tonicity, and/or preservation additives, is present in the diluted corticosteroid compositions containing TPGS in an amount of at least about 70, preferably at least about 80, more preferably at least 90, and even more preferably at least about 95, percent by weight. The various other additives, such as buffers, tonicity adjusting agents, and preservatives, are preferably blended into the compositions as part of the aqueous phase, and the use of the term "aqueous phase" is intended to include such components, if used.

It has been found that the inclusion of any one of a group of cosolvents in these TPGS corticosteroid compositions can aid in the processing of the compositions and in the solubilizing of the drug. Preferred cosolvents include mono- and polyvalent alcohols, such as propylene glycol, ethanol, glycerol, glycofurol (available as Tetraglycol from Sigma), ethoxydiglycol (available as Transcutol from Gattefossé), and polyethylene glycol (PEG) having an average molecular weight between about 200 and 4000, preferably between 200 and 1000, more preferably PEG 400, and combinations thereof. The cosolvents can be present individually in the final, diluted corticosteroid compositions in

for TPGS.

The corticosteroid compositions can contain other high-HLB surfactants, such as ethoxylated hydrogenated castor oil (Cremophor RH40 and RH60, available from BASF), tyloxapol, sorbitan esters such as the Tween series (from ICI Surfactants) or the Montanox series (from Seppic), etc. The corticosteroid compositions preferably contain either, or both, of the ethoxylated derivatives of vitamin E or the polyethylene glycol fatty acid esters as all or part of the high-HLB surfactant component, and in general the sum of these two types of surfactants will account for at least 50%, preferably at least 75%, and more preferably at least 90% by wt. of the high-HLB surfactant component.

Optionally, low HLB surfactants, having an HLB value below about 8, can also be used in the present invention. Examples of such low HLB surfactants include phospholipids, such as phosphatidylethanolamine, phosphatidylcholine, and phosphatidylinositol; and medium-chain mono- and diglycerides, i.e., mono- and di-glycerides of C_8 to C_{12} fatty acids, and mixtures thereof. The low HLB surfactants can be used in general at levels from about 0.1 to about 3 percent by weight in the diluted composition.

Optionally, an oil can also be incorporated into the compositions. Examples of pharmaceutically acceptable oil compounds include triglycerides and propylene glycol diesters of C_8 to C_{12} fatty acids such as the Captex series available from Abitec. Oils can be used in general in levels from about 1 to about 30 percent by weight in the concentrated compositions and from about 0.1 to about 3 percent by weight in the diluted composition.

It is necessary to add the drug to the compositions containing high-HLB and low HLB surfactants, and/or cosolvents, and/or the oil compounds, to form the concentrated corticosteroid compostion prior to dilution with the aqueous phase.

The diluted corticosteroid compositions using high-HLB surfactants such as TPGS or Solutol HS-15 to solubilize the drug are believed to be micellar compositions. This belief is based on the fact that the critical micelle concentration for both TPGS and Solutol HS-15 is about 0.02% by weight at 37°C, which is below their concentration in the diluted corticosteroid compositions. If an oil component is present with or without a low HLB surfactant, an oil-in-water (o/w) microemulsion may be formed as the diluted corticosteroid composition.

saline, malate buffer, citrate buffer, phosphate buffer, and 5% solutions of propylene glycol, PEG 200, or PEG 400 in any of the above. These diluted compositions were blended until any gel that may have formed when the TPGS concentrate came into contact with the aqueous phase was completely dispersed. Transparent, physically stable, diluted corticosteroid compositions without any precipitates were obtained containing about 28 to 420 μg/ml beclomethasone dipropionate. The diluted corticosteroid compositions were sterilized by passing them through a 0.22 micron sterile filter.

Example 2

Beclomethasone dipropionate monohydrate (4.2 mg) was dissolved in 995.8 mg of a binary liquid mixture of TPGS and ethanol (1:1 weight ratio) by briefly mixing at room temperature to form a concentrated corticosteroid composition. The concentrate was diluted 1:100 by volume in solutions of 5 wt.% PEG 400 in either deionized water, saline, or 20 mM malate, citrate, or phosphate buffer, by mixing for several minutes at room temperature. The resulting optically transparent, diluted corticosteroid compositions contained about 42 μg beclomethasone dipropionate per ml. The diluted corticosteroid compositions were sterilized by passing them through a 0.22 micron sterile filter.

The same concentrated corticosteroid composition was also diluted 1:50 by volume in the above-mentioned aqueous phases, and resulted in final formulations containing about 84 μg beclomethasone dipropionate per ml. These diluted formulations were physically and chemically stable for over a year at 5°C, 25°C/60% RH and 40°C/75% RH.

Example 3

Several corticosteroids – beclomethasone dipropionate, budesonide, and triamcinolone acetonide – were dissolved in binary mixtures of TPGS and a cosolvent selected from the group of ethanol, propylene glycol, PEG 200 and PEG 400. The weight ratio of TPGS to cosolvent was 1:1, and the resulting drug concentrations were between 1.4 and 4.0 mg/gram. It was necessary to heat the TPGS/propylene glycol and the TPGS/PEG mixtures to approximately 45°C for several minutes in order to dissolve the drugs, but dissolution could be achieved in the TPGS/ethanol mixture at room

Component	Form. 1	Form. 2	Form. 3	Form. 4
Beclomethasone dipropionate	42 μg/g	42 μg/g	42 μg/g	42 μg/g
TPGS	1%	1%	0.5%	0.5%
Polyethylene glycol 400	.....	1%	5%	5%
Ethyl Alcohol (190 Proof)	.....	.....	0.5%	0.5%
Deionized Water	q.s.	q.s.	q.s.	.....
0.9% NaCl Solution	.....	.....	.....	q.s.

Formulations were stored in glass vials and blow-molded polyethylene ampules for the duration of the study. Various tests were used to assess the physical and chemical stability of the corticosteroid compositions given above.

Size and distribution of the dispersed material droplets in the aqueous solution of the above compositions were determined using a quasi-elastic light scattering technique. The experimental equipment consisted of a BI-200SM Goniometer and BI9000AT Digital Correlator from Brookhaven Instrument Corporation, and a Thorn EMI Electron tube for detection powered by a high voltage power supply, delivering 2000 volts, from Bertan Associates. A helium-neon laser from Spectra Physics was the light source, with a wavelength of 632.8 nm. The droplet size of the dispersed phase in all formulations before nebulization was about 10 nm, and remained constant for the duration of the study.

The MMAD and the corresponding geometric standard deviation (GSD) of the nebulized corticosteroid compositions were determined at time zero of the study. Saline was used as a reference. The experiments were done using a system consisting of a Proneb compressor and a Pari LC Plus Reusable Nebulizer (Pari Respiratory Equipment, Inc., Richmond, VA) equipped with an adapted mouthpiece, connected in series with an Andersen cascade impactor (Andersen Airsampler Inc., Atlanta, GA). A vacuum pump was connected to the outlet of the cascade impactor, and between them was an air flow controller which indicated a flow of about 28.3 L/min. A cascade impactor is a mechanical model of human lung, containing seven stages and a filter before the outlet, which represent increasing depths of penetration. The amount of excipients deposited on each plate was determined by the increase in the plate dry weight. Analogous results were obtained when determining the MMAD from the drug mass on each plate. This showed

Examples 6 through 8 describe additional compositions suitable for inhalation.

Example 6

These budesonide formulation compositions are suitable inhaled delivery compositions:

Component	Formulation 1	Formulation 2
Budesonide	100 µg/g	100 µg/g
TPGS	1 %	1 %
Propylene glycol	1.72 %	------
Polyethylene glycol 400	------	1 %
Sodium chloride	------	0.65 %
Citrate Buffer	97.27%	97.34%

Formulation 1 was prepared as the follows: a mixture of melted TPGS and propylene glycol in a weight ratio of 1:1.72 was first prepared at 45 to 50°C, then the resulting liquid concentrate was cooled to ambient temperature. Budesonide was then added and dissolved at ambient temperature. The concentrate was diluted at room temperature in 20 mM citrate buffer at pHs of 3.5, 4.0 and 4.5.

Formulation 2 was prepared similarly to formulation 1 with a mixture of melted TPGS and PEG 400 with a weight ratio of 1 to 1. The budesonide was dissolved by stirring at 35 to 40°C. The mixture was slightly warmed to reduce viscosity. Alternatively, budesonide will dissolve at room temperature by using appropriate mechanical mixing equipment. The resulting concentrate was then diluted at ambient temperature into solutions of 20 mM citrate buffer with the above pHs containing sodium chloride to adjust the tonicity.

After dilution all samples were sterilized by filtering them through a 0.2 µm Millipore sterile filters and placed in sterile low density polyethylene plastic vials. These formulations were kept in humidity and temperature controlled chambers at 5° C 25°C/60% RH and 40°C/75% RH (where RH is the relative humidity). The % recovery after 13.5 weeks from time zero is presented for each formulation and storage condition, in the following table:

	Formulation 1 (Budesonide 500 µg/g - 3% TPGS)	Formulation 2 of Ex. 6 (Budesonide 100 µg/g -1% TPGS)
MMAD (µm)	2.15	2.26
GSD	2.75	2.76
Respirable Fraction (%)	63.3	61.8

Both the MMAD data and the respirable fraction data support the utility of these formulations for delivery of budesonide to the lung by way of inhalation. These formulations can also be used for nasal delivery using a spray device, preferably with the preservatives.

The amount of 0.4 g of Fluticasone 17-propionate was added to 79.6 g of melted TPGS and a mixture was stirred at 60°C until homogeneous (approximately 1 hr). The concentrate was diluted (1:10 wt/wt) with an aqueous phase consisting of 0.01 M citrate buffer, sodium chloride, benzalkonium chloride and disodium edetate. The mixture was stirred at 60°C for 20 minutes (until homogeneous). The composition of the formulation is given in the following table.

Component	**Weight Percent** Concentrate mixture	**Wt/Wt Percent** After 1:10 Dilution
TPGS	99.5	9.950
Fluticasone 17-propionate	0.5	0.050
Sodium chloride	-	0.612
Benzalkonium chloride	-	0.020
Disodium edetate	-	0.050
0.01 M citrate buffer, pH 5	-	89.318

Example 11

This example contains two corticosteroid compositions that form oil-in-water microemulsions after dilution of the concentrate with an aqueous phase.

Fluticasone 17-propionate (38.5 mg) was dissolved in 9.9615 g of a mixture of TPGS-Captex 300 (9:1 by weight) by stirring for 1 hour at 60°C. The concentrate was diluted (1:35 wt/wt) with 0.01 M citrate buffer containing 1.8% propylene glycol as an osmolality adjuster by stirring for 10 minutes at 60°C. The composition of the final transparent formulation is given in the following table.

Component	**Weight Percent** Concentrate mixture	**Wt/Wt Percent** After 1:35 Dilution
TPGS	89.6535	2.5623
Captex 300	9.9615	0.2847
Fluticasone 17-propionate	0.385	0.011
Propylene glycol	-	1.7486
0.01 M citrate buffer, pH 5	-	95.3934

What is claimed is:

1. A composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, consisting essentially of:

(a) from 5 μg/ml to about 5 mg/ml of a corticosteroid in dissolved form;

(b) from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component, wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E; and

(c) at least about 70 weight percent aqueous phase.

2. Cancel.

3. Cancel.

4. Cancel.

5. The composition of claim 1 wherein the corticosteroid comprises beclomethasone dipropionate.

6. The composition of claim 1 wherein the corticosteroid comprises budesonide.

7. The composition of claim 1 wherein the corticosteroid comprises triamcinolone acetonide.

15. The composition of claim 12 further comprising from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable cosolvent comprising propylene glycol, polyethylene glycol having a molecular weight between about 200 and 4000, glycerol, ethoxydiglycol, glycofurol, and ethanol, or a combination thereof.

16. The composition of claim 12 further comprising from about 0.1 to about 3 percent by weight of a low HLB surfactant having an HLB below about 8.

17. The composition of claim 12 further comprising from about 0.1 to about 3 percent by weight of an oil.

18. A method for administering a therapeutic dosage of a corticosteroid to the respiratory tract, comprising:

(a) providing a corticosteroid composition comprising:

(1) from 5 μg/ml to about 5 mg/ml of a corticosteroid in dissolved form;

(2) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50 percent by weight of an ethoxylated derivative of vitamin E; and

(3) at least about 70 weight percent aqueous phase;

(b) aerosolizing the corticosteroid composition; and

(c) administering a therapeutic effective dosage of the aerosol of the corticosteroid composition by inhalation.

19. The method of claim 18 wherein the corticosteroid composition consists essentially of said corticosteroid, said aqueous phase, and said high-HLB surfactant.

20. A method for administring a therapeutic dosage of a corticosteroid to the nasal passage, comprising:

(a) providing a corticosteroid composition comprising:

(1) from about 50 μg/ml to about 10 mg/ml of a corticosteroid in dissolved form,

(2) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants is greater than about 10, and wherein the high-HLB surfactant component comprises an ethoxylated derivative of vitamin E, a polyethylene glycol fatty acid ester, or a mixture thereof; and

(3) at least about 70 weight percent aqueous phase;

(b) administering a therapeutic effective dosage of the corticosteroid composition by nasal inhalation.

21. A method of preparing a diluted corticosteroid composition containing the corticosteroid in a relatively high, dissolved concentration, comprising:

(a) dissolving a corticosteroid compound into a molten pharmaceutically acceptable high-HLB surfactant component, wherein the HLB of the high-HLB surfactant component is greater than about 10;

(b) subsequently blending the molten high-HLB surfactant component containing the dissolved corticosteroid with an aqueous phase,

wherein the aqueous phase is present in an amount of at least about 70 weight percent, and the high-HLB surfactant component is present in an amount of from about 0.1 to about 20 weight percent of the diluted corticosteroid composition.